Remarks/Arguments

Claims 1, 3-8, 10-12, 15-17, 21, 24-25, 36, and 37, as amended, are pending in the application for the Examiner's review and consideration. Claims 2, 9, 13-14, 18-20, 22, 23 and 26-35 have been canceled without prejudice. The right to prosecute the subject matter of any of the canceled claims in this or in a continuation, continuation-in-part, or divisional application is hereby expressly reserved.

I. Summary of Interview

The undersigned appreciates the courtesies extended to her and her colleague Esther Kepplinger, Reg. No. 57,243, by Examiners Johann Richter and Frank Choi in the personal Interview of July 29, 2009. In the Interview, the rejections of the claims under 35 U.S.C. § 103(a) were discussed, and the Examiners stated that an amendment of claim 1 to exclude tyrosine would overcome Schinitsky & Meisner. The Examiners also acknowledged that Applicant's arguments with respect to the non-obviousness of the heating step and the pH recited in the claims have some merit.

Other topics discussed in the Interview are included in the Remarks that follow.

II. Claim Amendments

Claim 1 has been amended to recite that the composition does not comprise tyrosine, as the Examiners suggested in the Interview of July 29, 2009. This amendment is supported, for example, on page 8, lines 9-17 of the specification as filed, which recites the optional inclusion of tyrosine in the composition. "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." M.P.E.P. § 2173.05(i).

New claim 37 has been added. Claim 37 is supported, for example, on page 7, lines 4-8 of the specification as filed.

No new matter has been added to the claims by these amendments.

III. Declaration of Dr. Lorraine Faxon Meisner

As requested by the Examiners in the Interview of July 29, 2009, submitted herewith for the Office's consideration is a copy of the Declaration of Dr. Lorraine Faxon Meisner under 37

C.F.R. § 1.132 that was filed on April 9, 2009 in connection with co-pending U.S. application Serial No. 12/015,258 ("Meisner Declaration").

IV. Claim Rejections – 35 U.S.C. § 103

Claims 1, 3-8, 10-12, 15-17, 21, 23-25, and 36 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,938,969 to Schinitsky and Meisner ("Schinitsky & Meisner") in view of U.S. Patent No. 5,804,594 to Murad ("Murad"); U.S. Patent No. 5,902,591 to Herstein ("Herstein") or U.S. Patent No. 5,140,043 to Darr and Pinnell ("Darr"); THE MERCK INDEX, entry 855 (9th ed. 1976) ("Merck Index"); and J.P. Yuan & F. Chen, *J. Agric. Food Chem.*, 46: 5078-82 (1998) ("Yuan"). These rejections have been rendered moot as to claim 23 by its cancellation without prejudice. As to claims 1, 3-8, 10-12, 15-17, 21, 24-25, and 36, and new claim 37, these rejections are respectfully traversed for the reasons discussed below.

The claims recite topical compositions comprising about 5% to about 25% (w/v) ascorbic acid; a non-toxic zinc salt; and water, wherein the composition has a pH of about 3.5 to about 4.1; the composition does not comprise tyrosine; and the composition is prepared by a process comprising: (a) dissolving about 10% to about 50% of the ascorbic acid in water at a temperature of between about 60°C to about 90°C to provide an aqueous ascorbic acid solution of at least 20% (w/v); (b) cooling the aqueous ascorbic acid solution to below about 40°C; (c) combining the aqueous ascorbic acid solution with water, a non-toxic zinc salt, and ascorbic acid to provide a mixture comprising water, a non-toxic zinc salt, and about 5% to about 25% (w/v) ascorbic acid; and (d) adjusting the pH of the mixture to about 3.5 to about 4.1.

A. The primary reference Schinitsky & Meisner fails to disclose or provide any guidance as to each and every recitation of the claims

Schinitsky & Meisner refers to a composition for topical application to reduce epidermal wrinkling resulting from intrinsic aging or photo-aging, which comprises from about 2 to about 20% ascorbic acid, about 1 to about 10% tyrosine, and about 0.5 to about 5% zinc sulfate in a pharmaceutically acceptable vehicle. (Schinitsky & Meisner, col. 2, ll. 38-53).

Schinitsky & Meisner fails to disclose or provide any guidance as to a composition that does not comprise tyrosine, as recited in the claims. To the contrary, every composition referred to in Schinitsky & Meisner contains tyrosine as an ingredient. Thus the elimination of tyrosine

as a component of the composition, as discussed during the Interview of July 29, 2009, distinguishes over the primary reference and the rejection.

Further, Schinitsky & Meisner fails to disclose or provide any guidance as to a composition that has a pH of about 3.5 to about 4.1. In fact, Schinitsky & Meisner is completely silent as to pH.

Further still, Schinitsky & Meisner fails to disclose or provide any guidance as to a composition comprising ascorbic acid that has been prepared by the process recited in the claims. Again, Schinitsky & Meisner is completely silent as to the process used to prepare the compositions.

B. The secondary references cited by the Office fail to remedy the deficiencies of the primary reference Schinitsky & Meisner

The Office cites Murad, Merck Index, Yuan, and Herstein or Darr in order to remedy the above-described deficiencies of Schinitsky & Meisner. This, however, is unavailing at least because none of the secondary references, either alone or in combination, discloses or provides any guidance as to the recited process used to prepare the compositions of the claims. The recited process imparts properties to the claimed compositions that are not taught by and cannot be achieved by the compositions of the prior art.

Murad fails to disclose or provide any guidance as to a composition comprising ascorbic acid that has been prepared by the process recited in the claims. Murad simply states that the compositions may be prepared by "any of the methods of pharmacy." (Murad, col. 9, ll. 34-49). Further, Murad fails to disclose or provide any guidance as to a composition that has a pH of about 3.5 to about 4.1. Like Schinitsky & Meisner, Murad is completely silent as to pH.

1. "(a) dissolving about 10% to about 50% of the ascorbic acid in water at a temperature of between about 60°C to about 90°C to provide an aqueous ascorbic acid solution of at least 20% (w/v); (b) cooling the aqueous ascorbic acid solution to below about 40°C"

The Office cites Merck Index and Yuan to provide the missing teaching of the steps of "(a) dissolving about 10% to about 50% of the ascorbic acid in water at a temperature of between about 60°C to about 90°C to provide an aqueous ascorbic acid solution of at least 20% (w/v)" and "(b) cooling the aqueous ascorbic acid solution to below about 40°C."

Merck Index refers to the compound ascorbic acid and states that the solubility of ascorbic acid in hot water is "80% at 100°; 40% at 45°." Merck Index does not disclose or provide any guidance as to a topical composition comprising ascorbic acid, or as to a method for preparing such a topical composition that includes steps (a) and (b) above. At most, Merck Index teaches the person of ordinary skill in the art that ascorbic acid has a particular solubility in water at 100°C and 45°C. The Merck Index does not provide any suggestion of what the solubility of the ascorbic acid would be once the solution cools and based on the information given in Merck about the two temperatures, one would expect the solubility to decrease along with the temperature. Moreover, there is no suggestion of increased stability stemming from the recited preparation. Thus, there would be no motivation, except hindsight reconstruction, to heat and cool as recited in the present claims.

Yuan refers to experiments in which solutions of ascorbic acid in aqueous media at pH 4 were heated at 60°C or 100°C for 2 hours. (Yuan, p. 5079 and Figure 1). Yuan reports the presence of at least three degradation products of ascorbic acid in each solution after heating: furfural; 3-hydroxy-2-pyrone; 2-furoic acid (only in the solution heated at 100°C); and an unknown compound. (Yuan, p. 5081-82). Yuan does not disclose or provide any guidance as to a topical composition comprising ascorbic acid, or as to a method for preparing such a topical composition that includes steps (a) and (b) above. To the contrary, Yuan teaches away from heating ascorbic acid at a temperature of between about 60°C to about 90°C, as recited in the claims, by showing that heating ascorbic acid at 60°C or 100°C causes the ascorbic acid to degrade. The person of ordinary skill in the art would recognize that it is not desirable (and often not permitted by the U.S. Food and Drug Administration) to have degradation products in a composition for pharmaceutical use, such as that recited in the present claims.

Therefore, neither Merck Index nor Yuan, when combined with the teachings of Schinitsky & Meisner and Murad, discloses or provides any guidance as to topical compositions of ascorbic acid made by a process including steps (a) and (b) above, as recited in the claims.

2. **"(d) adjusting the pH of the mixture to about 3.5 to about 4.1"**

The Office cites Darr or Herstein to provide the missing teaching of the step of adjusting the pH of the mixture to about 3.5 to about 4.1.

As discussed in the Meisner Declaration submitted herewith, at the time of the invention, it would have been entirely unexpected that an ascorbic acid composition would be stable enough for use in a topical composition at a pH of about 3.5 to about 4.1. (Meisner Declaration, ¶¶ 11-12). Dr. Meisner's conclusion is supported not only by the Bauernfeind, Hajratwala, and Kassem articles cited in her Declaration, but also by Darr and Herstein as described below, which were cited by the Office.

Darr refers to a stable topical composition which consists essentially of at least about 1 wt. % ascorbic acid in water and a carrier for topical application, where the pH of the composition is no more than about 3 to 3.5, and preferably no more than about 2.5. (Darr, col. 3, ll. 18-32). Despite Darr's emphasis on compositions having pH below 3.5, the Office selects and relies upon the following statement in Darr to provide a teaching of pHs in the range of those in the present claims: "even at relatively high pH's [pHs up to 5], the L-ascorbic acid at a 5% concentration is quite stable." (Darr, col. 5, ll. 1-13 and Figure 3). This statement was taken from Darr's Example III, which describes an experiment where ascorbic acid compositions were stored for 6 to 12 weeks in the dark, at low temperature (4°C), in capped microfuge tubes. Thus, Darr does not disclose ascorbic acid compositions above pH 3.5 that are stable under standard storage conditions. Accordingly, Darr would not guide the person of ordinary skill in the art to formulate an ascorbic acid composition having a pH of about 3.5 to about 4.1 in order to arrive at a topical composition as recited in the claims.

Herstein refers to stable topical emulsions for cosmetic/pharmaceutical purposes comprising a powdered ascorbic acid phase and a liquid phase, the liquid phase containing an emulsion stabilizingly effective amount of an organoclay material. (Herstein, abstract). The Office states that Herstein "discloses that a pH within 3.5 to 4.1 is preferred to facilitate entry of ascorbic acid into the skin." (Office Action, p. 4). Herstein, however, also acknowledges the instability of ascorbic acid at a pH of 3.5 to 4.1, stating that "[w]ithout the organoclay ingredient, the emulsion would begin to break down after a few days, i.e., 2-3 days." (Herstein, col. 13, ll. 37-39).

In the Interview of July 29, 2009, the Examiner pointed out that Figure 5 of Yuan appears to contradict the conclusions of Dr. Meisner, Bauernfeind, Hajratwala, Kassem, Herstein, and Darr, and requested that the Applicant explain the alleged contradiction in this Response. Figure

5 of Yuan purports to show the effect of pH on the contents of four degradation products of ascorbic acid after heating at 100°C. The total content of the four degradation products appears to be at a minimum around pH 4 in Figure 5. It is respectfully submitted that this result is inapposite because the claims do not require heating an ascorbic acid solution at pH 4. The claims recite the steps of: (a) dissolving about 10% to about 50% of the ascorbic acid in water at a temperature of between about 60°C to about 90°C to provide an aqueous ascorbic acid solution of at least 20% (w/v); (b) cooling the aqueous ascorbic acid solution to below about 40°C; . . . and (d) *adjusting the pH of the mixture to about 3.5 to about 4.1.* According to the specification, the pH of the ascorbic acid solution during heating is about 2.0 to 2.5. (Specification as filed, p. 7, ll. 4-6). Referring to Figure 5 of Yuan, there are significant amounts of degradation products (especially 3-hydroxy-2-pyrone) produced when heating a pH 2.0-2.5 ascorbic acid solution at 100°C. Thus, Yuan, like Bauernfeind, Hajratwala, Kassem, Darr, and Herstein, teaches away from the method recited in the claims.

Moreover, neither Darr nor Herstein discloses or provides any guidance as to steps (a) and (b) of the preparation process recited in the claims in order to achieve a composition of ascorbic acid having a pH of 3.5 to 4.1.

Therefore, neither Darr nor Herstein, when combined with the teachings of Schinitsky & Meisner, Murad, Merck Index, andYuan discloses or provides any guidance as to topical compositions of ascorbic acid made by a process including steps (a), (b), and (d) above, as recited in the claims.

For these reasons, the Office has failed to make out a *prima facie* case of obviousness of the claims. Accordingly, the rejections of claims 1, 3-8, 10-12, 15-17, 21, 23-25, and 36 under 35 U.S.C. § 103 as obvious over Schinitsky & Meisner in view of Murad, Herstein or Darr, Merck Index, and Yuan cannot stand and should be withdrawn.

Conclusion:

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims are in condition for allowance. Early and favorable action by the Examiner is earnestly

solicited. If any outstanding issues remain, the Examiner is invited to contact the undersigned at (212) 497-7731 to discuss the same before issuing a further Action.

No fee is believed to be due for the submission of this Amendment. Should any fees be required, please charge all such fees to Wilson, Sonsini, Goodrich & Rosati Deposit Account No. 23-2415 (36091-701.302).

Respectfully submitted,

Dated: October 7, 2009

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